

## **Exhibit 3**

### **Translation of the Kengo reference**

Kenjo

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## DETAILED DESCRIPTION

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### [Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the eating-and-drinking article which has the prevention or the improvement operation of a medical symptom resulting from the hypertension or it which comes to add the extract which uses a dioxo bicyclo [3.3.0] octane derivative or this derivative as a principal component at the preventive of the medical symptom resulting from the hypertension or it which makes an active principle a dioxo bicyclo [3.3.0] octane derivative and an improvement agent, and a list, and its manufacture approach.

[0002]

[Description of the Prior Art] Although blood pressure calls a continuously high condition hypertension, about how many the above is made into hypertension, some differences of opinion are also among scholars. In WHO, it has decided as following from the epidemiological standpoint. That is, a normal range is made to 140/90 or less mmHg, and 160/95 or more mmHgs are made into hypertension. However, there are many people who consider clinically that maximal-blood-pressure 150mmHg and 90 or more mmHgs of diastolic blood pressures are hypertension with some corrections being required by age or the sex. By the youth, it may be regarded as hypertension below with this value.

[0003] Although there are various illnesses which cause hypertension, if it divides roughly, they will become the essential hypertension which is not clear, and secondary hypertension with a clear cause. As a disease which causes secondary hypertension, endocrinologic diseases, such as kidney disease, such as glomerulonephritis, pyelonephritis, and a renal artery stenosis, primary aldosteronism, Cushing's syndrome (all are adrenal cortical tumors), and a pheochromocytoma (adrenal medulla neoplasm), coarctation of the aorta, and a certain kind of a central nervous system disease and others are mentioned. On the other hand, there is most essential hypertension among hypertension and it occupies about 80%. It is unknown, and although the thing whose cause is current and a hereditary factor is [ the thing ] related is clarified, the detail of a heredity format is unknown.

[0004] The symptoms of essential hypertension are shown from 35-40 years-old time in many cases. At first, blood pressure is labile and everything but elevation of blood pressure does not show special \*\* and objective comment. With progress of the date, it becomes durability, ventriculus-sinister hypertrophy, arteriosclerosis, and arteriocardillary sclerosis happen, and hypertension causes ischemic failures, such as a brain, the heart, and the kidney. In this way, the cerebral hemorrhage, cerebral thrombosis, congestive heart failure, myocardial infarction, uremia, etc. are generated in a mature stage or old age, and it dies in it. Thus, it is the disease to which hypertension has a bad influence on the angiopathy in the disease about various blood vessels especially the heart, and a brain, and it is a problem important for today's medicine how this is prevented and treated.

[0005] In current, by remarkable development of a hypotensor, it is possible for hypertension [ serious illness how ] to also lower blood pressure, but on the other hand the problem which should be solved in respect of a side effect has accumulated. Since the pharmacotherapy over a long period of time (whole life) is needed, the therapy of hypertension has few especially side effects, and the drugs which are moreover more well effective are called for. Moreover, since a suitable hypotensor changes with people even if it is the same hypertension, the hypotensor of the type with which versatility differed is required. Furthermore, in the case of the hypertension which is not a serious illness so much, the mild hypotensor without a side effect is called for.

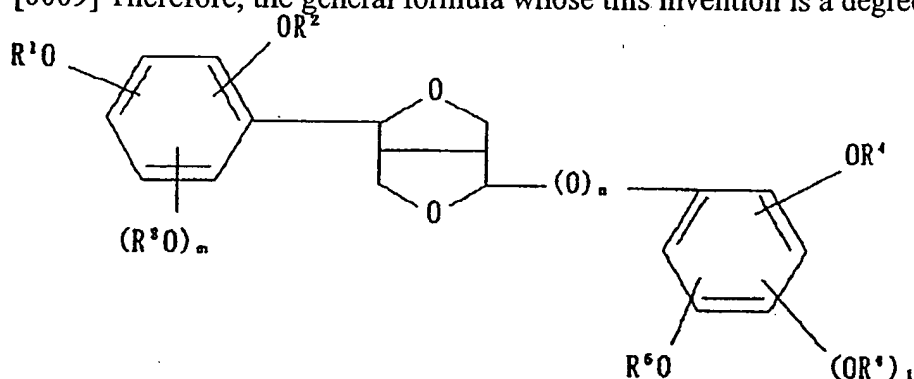
[0006] From such a viewpoint, retrieval research of what has the pressure-lowering effectiveness with medicinal herb extractives is done recently. Since such vegetable extractives pharmaceutical preparation does not almost have a side

effect unlike hypotensors, such as calcium antagonist and beta-blocker, it is thought that an important location is especially occupied in the application to self-medication. There are also many people who worry about the stress symptom in order to also call it a hypertension reserve in stress society especially like the present age. To such a person, safety is high and the crude drugs preparations which were moreover excellent in effectiveness are required. [0007]

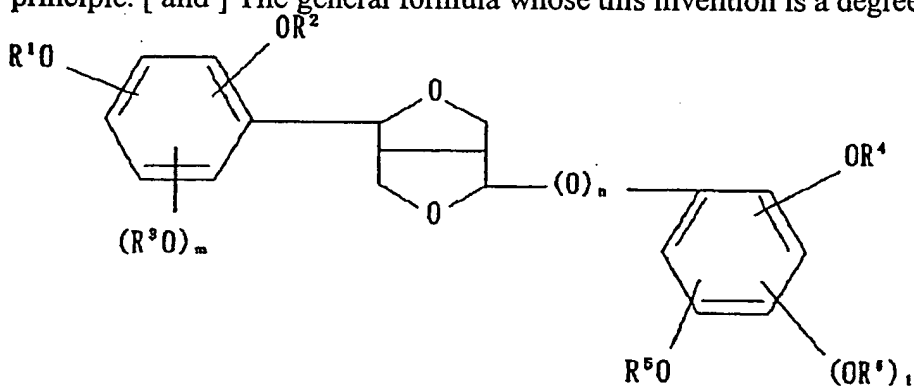
[Problem(s) to be Solved by the Invention] Therefore, this invention is extremely stable and it is going to provide the preventive of the medical symptom to which a side effect originates in little new hypertension or new it and an improvement agent, and a list with the eating-and-drinking article which has the prevention or the improvement operation of a medical symptom resulting from hypertension or it, and its manufacture approach. [0008]

[Means for Solving the Problem] In order that this invention person etc. may attain the above-mentioned purpose, as a result of studying many things, it extracted or isolated from a sesame seed, \*\*\*\*\*, or sesame oil, or the dioxabicyclo [3.3.0] octane derivative obtained by composition completed header this invention for it being effective in the prevention or the improvement of a medical symptom resulting from hypertension or it.

[0009] Therefore, the general formula whose this invention is a degree (I): It is [Formula 3].



(R1, R2, R3, R4, R5, and R6 are a hydrogen atom or the alkyl group of carbon numbers 1-3 independently among a formula, respectively.) Or R1 R2 and/or R4 R5 Become together and a methylene group or ethylene is expressed. n, m and l0, or 1 -- expressing -- it is going to offer the prevention or the improvement agent of a medical symptom resulting from the hypertension or it which comes to contain the dioxabicyclo [3.3.0] octane derivative expressed as an active principle. [ and ] The general formula whose this invention is a degree again (I): It is [Formula 4].



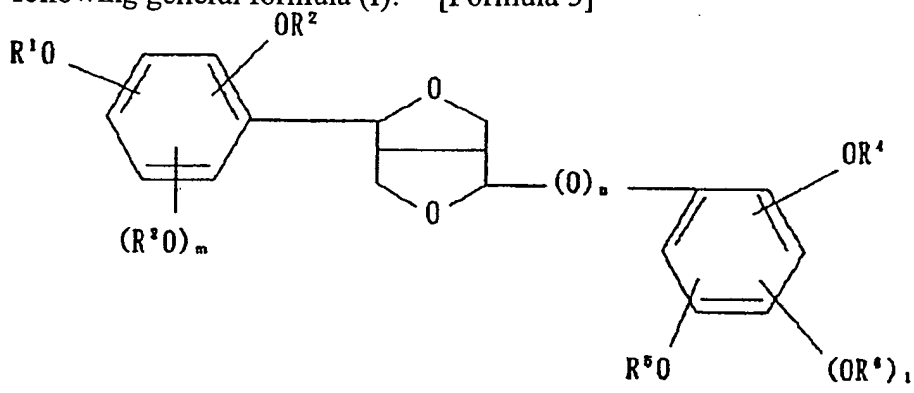
(R1, R2, R3, R4, R5, and R6 are a hydrogen atom or the alkyl group of carbon numbers 1-3 independently among a formula, respectively.) Or R1 R2 and/or R4 R5 Become together and a methylene group or ethylene is expressed. n, m and l0, or 1 -- expressing -- the dioxabicyclo [3.3.0] octane derivative expressed -- [ and ] Or it is going to offer the eating-and-drinking article which has the prevention or the improvement operation of a medical symptom resulting from the hypertension or it which comes to add the extract which uses this derivative as a principal component.

[0010] Furthermore, sesamin, SESAMI Norian, episesamin, EPISESAMI Norian, Sesamolin, 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0] octane, 2, 6-screw - (3-methoxy-4-hydroxyphenyl) -3, 7-dioxabicyclo [3.3.0] octane, And it is [0011] to the ingesta which do not contain 2-(3, 4-

methylenedioxyphenyl)-6-(3-methoxy-4-hydroxy phenoxy)-3 and 7-dioxabicyclo [3.3.0] octane on parenchyma. Sesamin, SESAMI Norian, episesamin, EPISESAMI Norian, sesamolin, 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0] octane, 2, 6-screw - (3-methoxy-4-hydroxyphenyl) -3, 7-dioxabicyclo [3.3.0] octane, Or 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxy phenoxy)-3, 7-dioxabicyclo [3.3.0] octane, Or it is going to offer the eating-and-drinking article which has the prevention or the improvement operation of a medical symptom resulting from the hypertension or it which is characterized by being independent, or mixing the extract which uses these one sort or two or more sorts as a principal component, and adding, and its manufacture approach.

[0012]

[Specific Explanation] the dioxabicyclo [3.3.0] octane derivative which is the active principle of this invention -- following general formula (I): -- [Formula 5]



(R1, R2, R3, R4, R5, and R6 are a hydrogen atom or the alkyl group of carbon numbers 1-3 independently among a formula, respectively.) R1 [ or ] R2 and/or R4 R5 It is the compound expressed. together -- becoming -- a methylene group or ethylene -- expressing -- n, m and l0, or 1 -- expressing -- here, [ and ] With the alkyl group of 1-3 carbon numbers, a methyl group, an ethyl group, n-propyl group, an isopropyl group, etc. can be mentioned.

[0013] Still more specifically Sesamin, SESAMI Norian, episesamin, EPISESAMI Norian, Sesamolin, 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0] octane, 2, 6-screw - (3-methoxy-4-hydroxyphenyl) -3, 7-dioxabicyclo [3.3.0] octane, Or compounds, such as 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxy phenoxy)-3 and 7-dioxabicyclo [3.3.0] octane, can be mentioned. These compounds may be the forms of a glycoside and the optically active substance is also contained in the invention in this application.

[0014] In this invention, it is independent or said dioxabicyclo [3.3.0] octane derivative (henceforth "the derivative of this invention") can be used combining two or more sorts. Moreover, in this invention, the derivative of this invention is not what was restricted to the high grade purification object, and can also use the extract (henceforth "the extract which uses the derivative of this invention as a principal component") which uses one sort of said dioxabicyclo [3.3.0] octane derivative, or two or more sorts as a principal component. The extract which uses the derivative of this invention as a principal component can be extracted from the natural product containing the derivative of this invention according to a conventional method. As a natural product containing the derivative of this invention, the by-product of sesame oil, \*\*\*\*\*, and a sesame oil manufacture process, a sesame seed, Acanthopanax gracilistylus W.W. Smith, Kiriki, a white fruit tree hide, Piper longum, Asiasari radix, etc. can be mentioned. The content of the derivative of this invention of the extract which uses the derivative of this invention as a principal component has 5.0 good % of the weight or more, and 2.0 % of the weight or more is [ the sum total of the content of sesamin and episesamin ] moreover, especially more preferably preferably desirable [ a content / 1.0% of the weight or more ] 0.1% of the weight or more 0.5% of the weight or more preferably 0.05% of the weight or more.

[0015] For example, in order to obtain the extract which uses the derivative of this invention as a principal component from sesame oil, sesame oil is nonmiscible substantially and extract and concentration of the derivative of this invention can be done using the various organic solvents (for example, an acetone, a methyl ethyl ketone, a diethyl ketone, a methanol, ethanol, etc.) which can extract and dissolve. After mixing sesame oil and either of the above-mentioned solvents to homogeneity as the example, It puts in low temperature, phase separation is performed according to conventional methods, such as centrifugal separation, and the approach of acquiring by carrying out evaporation

removal of the solvent from a solvent fraction is mentioned. Still more specifically After melting sesame oil to the acetone of capacity six to 8 times preferably two to 10 times, it is left at -80 degrees C overnight, as a result, an oil component is precipitating, an acetone is distilled out of the filtrate obtained by filtration, and the extract which uses the derivative of this invention as a principal component is obtained.

[0016] After mixing sesame oil, a heat methanol, or heat ethanol, it puts in a room temperature and the approach of acquiring by carrying out evaporation removal of the solvent from a solvent fraction is mentioned. Moreover, still more specifically After mixing sesame oil violently [ it is desirable and ] two to 10 times at the heat methanol (50 degrees C or more) or heat ethanol (50 degrees C or more) of five to 7 time capacity, According to conventional methods, such as standing or centrifugal separation, phase separation is performed at a room temperature, a solvent is distilled out of a solvent fraction, and the extract which uses the derivative of this invention as a principal component is obtained. Furthermore, the extract which uses the derivative of this invention as a principal component using a supercritical gas extract can also be obtained.

[0017] The sesame oil to be used may be a refined material, or may be which crude material in front of a decolorization process in the manufacture process of sesame oil. Moreover, using the solvent of arbitration, for example, the same solvent as being used in the extract from the above-mentioned sesame oil, in order to obtain the extract which uses the derivative of this invention as a principal component from a sesame seed or \*\*\*\*\* (a cleaning sesame seed, residual oil 8 - 10% per part), after crushing a sesame seed or \*\*\*\*\* as occasion demands, it can extract with a conventional method. After separating extract residue, an extract is obtained by removing a solvent from an extract by evaporation etc.

[0018] The derivative of this invention can isolate the target compound from the sesame oil extract prepared by the above-mentioned approach etc., defatted sesame seed residuum extract, or a sesame seed extract by processing according to conventional methods, such as a column chromatography, high performance chromatography, recrystallization, distillation, and a \*\*\*\* alternating current partition chromatography. A methanol/water (60:40) is still more specifically used for an opposition column (5C10) and an eluate. After isolating the above-mentioned extract preparatively with high performance chromatography and distilling off a solvent, The obtained crystal by recrystallizing by ethanol Sesamin, episesamin, SESAMI Norian, EPISESAMI Norian, sesamol, 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0] octane, 2, 6-screw - (3-methoxy-4-hydroxyphenyl) -3, 7-dioxabicyclo [3.3.0] octane, Or the derivative of this inventions, such as 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxy phenoxy)-3 and 7-dioxabicyclo [3.3.0] octane, is obtained. In addition, the approach and the purification approach of obtaining the extract which uses the derivative and this derivative of this invention as a principal component are not restricted to these.

[0019] Moreover, the derivative of this invention can also be obtained by composition according to a conventional method. For example, about sesamin and episesamin, it is compoundable by approach [J.Am.Chem.Soc.78 of Beroza and others, and 1242(1956)], and also PINORESHI Norian (it sets to a general formula (I) and is  $R_1 = R_4 = H$ ,  $R_2 = R_5 = CH_3$ , and  $n=m=l=0$ ) By Freudentberg's and others approach (Chem.Ber., and [86, 1157] (1953)) SHIRINGARESHI Norian (it sets to a general formula (I) and is  $R_1 = R_4 = H$ ,  $R_2 = R_3 = R_5 = R_6 = CH_3$ ,  $n=0$ , and  $m=l=1$ ) is compoundable by Freudentberg's and others approach (Chem.Ber., and [88, 16] (1955)).

[0020] The extract which furthermore uses the derivative or this derivative of this invention as a principal component can be used combining an anti-oxidant. As an anti-oxidant, for example Tocopherols, a flavone derivative, and FIROZURUSHIN kojic acid, a gallic-acid derivative, catechins, and Japanese butterbur -- an acid, a gossypol, and a pyrazine derivative -- Sesamol, guaiacol, guaiac resin, p-coumarinic acid, Norian dihydroguaiaretic acid, A natural anti-oxidant like sterols, terpenes, nucleobases, and carotinoids, Or butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), A synthetic anti-oxidant which is represented by a mono-tertiarybutyl hydroquinone (TBHQ), 4-hydroxymethyl -2, and 6-G tertiarybutyl phenol (HMBP) can be mentioned.

[0021] Also especially in an anti-oxidant, tocopherols are desirable and it can mention the alpha-tocopherol, the beta-tocopherol, the gamma-tocopherol, delta-tocopherol, epsilon-tocopherol, xi-tocopherol, eta-tocopherol, tocopherol ester (tocopherol acetate etc.), etc. as tocopherols. Furthermore, beta carotene, canthaxanthin, astaxanthin, etc. can be mentioned by carotinoids. Although there is especially no limit about the derivative of this invention, and the rate of an anti-oxidant, below the 1000 weight sections of an anti-oxidant are desirable in combination, more than the 0.001 weight section to the derivative 1 weight section of this invention. The range of further 0.01 - the 100 weight sections is desirable, and the range of 0.029 - 40 weight section is still more desirable.

[0022] The extract which uses the derivative or this derivative of this invention as a principal component is effective in the prevention or the improvement of a medical symptom resulting from the hypertension of essential or secondary nature, or it, in order that a side effect may control the rise of blood pressure intentionally few. Moreover, as a medical symptom caused by hypertension, ischemic failures (for example, cerebral apoplexy, angina pectoris, myocardial infarction, etc.), such as ventriculus-sinister hypertrophy, arteriosclerosis, arteriocardillary sclerosis, a brain, the heart, and the kidney, the cerebral hemorrhage in a mature stage or old age, cerebral thrombosis, congestive heart failure, uremia, etc. can be mentioned. In addition, in this invention, with an improvement of a symptom, it is used in large semantics and the therapy of a disease is also included.

[0023] When using the derivative of this invention as drugs, an administration gestalt As long as internal use or parenteral administration is performed with sufficient convenience, you may be the thing of what kind of dosage forms. For example, a parenteral solution, \*\*\*\*, powder, a granule, a tablet, a capsule, an enteric coated medicine, troches, Mixtures for internal use, suspension, an emulsion, syrups, liquids for external use, fomentations, a nasal drop, ear drops, ophthalmic solutions, inhalations, an ointment, lotions, suppositories, etc. can be mentioned, according to a symptom, it is independent, respectively, or these can be combined and used.

[0024] These various pharmaceutical preparation can be pharmaceutical-preparation-ized using the known adjuvant which can usually be used for a chief remedy in medicinal pharmaceutical preparation technical fields, such as an excipient, a binder, antiseptics, a stabilizer, disintegrator, lubricant, and corrigent, according to the purpose according to a conventional method. For example, when preparing injections, the solubilizing agent for drugs, such as a nonionic surface active agent, can be used, nonionic surface active agents, such as POE (60) hydrogenated castor oil of 80 time capacity or POE sorbitan mono-olate, can be made to be still more specifically able to carry out the heating dissolution of the derivative of this invention, and it can prepare by diluting with a physiological saline. Moreover, an isotonicizing agent, a stabilizer, antiseptics, and an aponia-ized agent may be added suitably if needed.

[0025] Moreover, as external preparations, an ointment, cream pharmaceuticals, etc. can be prepared by the usual approach, using vaseline, paraffin, fats and oils, lanolin, macro gall, etc. as a basis. Moreover, although the dose changes with the purpose of administration, or an administration candidate's situations (sex, age, weight, etc.) Usually, in internal use, 1mg - 1mg - 2g 10g per day is the range of 1mg - 200mg still more preferably preferably as a total amount of the derivative of this invention to an adult. Moreover, in the case of parenteral administration, as a total amount of the derivative of this invention, it can adjust suitably and 0.1mg - 1g [ per day ] 0.1mg - 200mg can be preferably prescribed for the patient in 0.1mg - 100mg still more preferably.

[0026] Moreover, since the prevention or the improvement effect of a medical symptom resulting from the hypertension or it which the derivative of this invention has by prescribing the derivative of this invention for the patient with an anti-oxidant, especially tocopherols is reinforced, Although the dose of the derivative of this invention changes with the purpose of administration, or an administration candidate's situations (sex, age, weight, etc.) Usually, in internal use, 0.1mg - 0.1mg - 500mg 2g per day is the range of 0.1mg - 100mg still more preferably preferably as a total amount of the derivative of this invention to an adult. Moreover, in the case of parenteral administration, 0.01mg - 0.01mg - 50mg 200mg per day is the range of 0.01mg - 20mg still more preferably preferably as a total amount of the derivative of this invention. and the rate of a compounding ratio of the derivative of this invention, and an anti-oxidant -- the derivative 1 weight section of this invention -- receiving -- an anti-oxidant -- the 0.001 - 1000 weight section -- desirable -- the 0.01 - 100 weight section -- it is the range of 0.029 - 40 weight section still more preferably, and it can adjust suitably and a medicine can be prescribed for the patient.

[0027] the compound which found out the derivative of this invention from the inside of the conventional food, or its relative -- since it is a compound, excelling also from the field of safety is clear. Moreover, when pitching in successive games (internal use) of sesamin 2.14 g/day / kg is carried out for two weeks to the IRC male mouse of 7 weeks old, the symptom unusual in any way is clear also from having not accepted, either.

[0028] When using the extract which uses the derivative or this derivative of this invention as a principal component as an eating-and-drinking article, the gestalt The gestalt of the above-mentioned physic pharmaceutical preparation is sufficient. Moreover, solid or liquefied food or luxury goods, for example, a pan, noodles, boiled rice, and confectionary (a biscuit, a cake, and a candy --) Agricultural foods, such as chocolate, Japanese sweets, tofu, and its workpiece, sake, Fermented foods, such as medicinal drinks, mirin, vinegar, soy sauce, and bean paste, a dressing, Fats-and-oils food, such as mayonnaise, margarine, shortening, and edible oil and fat, \*\*\*\* food, such as yogurt, a hum, bacon, and a sausage, and boiled fish paste -- it may lift and you may be processing gestalten, such as drinks, such as

marine foods, such as heavens and a light, puffy cake made of ground fish, a fruit-juice drink, a soft drink, a sport drink, an alcoholic beverage, and tea.

[0029] Moreover, although the gestalt of the above-mentioned physic pharmaceutical preparation or an eating-and-drinking article is sufficient as the gestalt when using as health food and functional food, it is protein (although protein, such as milk protein with the high nutritive value which was able to take amino acid balance as a source of protein, soybean protein, and ovalbumin, is used most widely), for example. You may be the natural liquid food, the defined formula diet and the component nourishing food with which the saccharide and fat with which the mixture of an amino acid simple substance besides being the oligopeptide of these decomposition products and an albumen, soybean hydrolyzate, etc. is also used, a trace element, vitamins, an emulsifier, perfume, etc. were blended, and processing gestalten, such as drinkable preparations.

[0030] The eating-and-drinking article of this invention can carry out processing manufacture of the extract which uses the derivative or this derivative of this invention as a principal component at the food raw material which does not contain the derivative of this invention substantially according to requirements, in addition a general manufacturing method. the loadings -- the gestalt of dosage forms and food -- it is not limited especially although it changes with descriptions, and it is desirable 0.001 - 50% of generally. Moreover, the intake as health food and functional food is used for the prevention and the improvement to the medical symptom resulting from hypertension or it, can add the extract which uses the derivative or this derivative of this invention as a principal component to the food of the arbitration which does not contain the derivative of this invention substantially under the management of a dietitian based on a medical practitioner's dietary slip in the case of cooking of hospital diet, and can also give it to a patient with the gestalt of the functional food adjusted on that spot.

[0031] Although the ingesta which have not used sesame etc. as the raw material in this invention with the ingesta which do not contain the derivative of this invention substantially are mentioned Even if it is the ingesta which use sesame etc. as a raw material, the content of the derivative of this invention in the eating-and-drinking article of the last gestalt is ultralow volume. Per [ of the ingesta ] one-day intake and the total content of the derivative of this invention Less than 0.1mg, Preferably Per one-day intake of a thing 0.8mg or less or its ingesta, Sesamin, SESAMI Norian, episesamin, EPISSEAMI Norian, sesamol, 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0] octane, 2, 6-screw - (3-methoxy-4-hydroxyphenyl) -3, 7-dioxabicyclo [3.3.0] octane, The sum total of the content of 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxy phenoxy)-3 and 7-dioxabicyclo [3.3.0] octane Or less than 0.1mg, A thing 0.8mg or less is preferably contained in the ingesta which do not contain the derivative of this invention substantially.

[0032] As for the eating-and-drinking article of this invention, it is desirable to carry out the ingestion of 1mg - the 10g of 1mg - the 2g of the total amounts of the derivative of this invention in 1mg - 200mg still more preferably preferably per day as a standard for the purpose of the prevention improvement and health maintenance to the medical symptom resulting from hypertension or it. Furthermore in the eating-and-drinking article of this invention, the extract which uses the derivative or this derivative of this invention as a principal component Since an operation of the prevention improvement to the medical symptom resulting from the hypertension or it which the derivative of this invention has by taking in with an anti-oxidant, especially tocopherols, or health maintenance is reinforced, The range of 0.1mg - 2g of 0.1mg - 500mg of total amounts of the derivative of this invention is 0.1mg - 100mg still more preferably preferably per day as a standard. and the rate of a compounding ratio of the derivative of this invention, and an anti-oxidant -- the derivative 1 weight section of this invention -- receiving -- an anti-oxidant -- the 0.001 - 1000 weight section -- it is the range of 0.029 - 40 weight section still more preferably, and it is preferably desirable the 0.01 - 100 weight section and to carry out an ingestion.

[0033] in addition, although the derivative of this invention is not contained substantially, in adding the extract which uses the derivative or this derivative of this invention as a principal component to an anti-oxidant, especially the ingesta containing tocopherols The content ratio of the derivative and anti-oxidant of this invention in the eating-and-drinking article of the last gestalt the derivative 1 weight section of this invention -- receiving -- an anti-oxidant -- the 0.001 - 1000 weight section -- preferably, the 0.01 - 100 weight section and the extract which uses the derivative or this derivative of this invention as a principal component can be added so that it may become the ratio of 0.029 - 40 weight section still more preferably. Under the present circumstances, it is also possible to add an anti-oxidant further if needed. Next, an example explains this invention still more concretely.

[0034] 26 example 1. SD system male rats (weights 200-240g) were divided into three groups. Inner of three groups 2

groups equipped the left renal artery with the silver clip (bore of 0.2mm), produced 2K and 1C mold renal hypertension model, and usually divided them into the diet group (ten animals) and the sesamin diet group (11 animals). The diet group gave general diet (the commercial type NMF, oriental yeast), and the sesamin diet group usually gave the sesamin foods which blended the mixture (sesamin: 51.5%, episesamin: 47.8%, and dioxabicyclo [3.3.0] octane derivative: 1.1% of others) of the dioxabicyclo [3.3.0] octane derivative of this invention 1%. Remainder 1 group gave and bred general diet as a non-load group (five animals). It is tail cuff about the blood pressure of each group rat weekly. It measured using law. A result is shown in drawing 1.

[0035]

[Table 1]

表 1

	未負荷群	普通食群	セサミン食群
体重 (g)	398.20±11.83	302.30±16.44**	307.27±11.34**
心臓重量 (mg)	1074.80±40.29	1112.90±55.94	999.82±51.54
左心室重量+中隔重量 (mg)	728.40±29.73	816.10±39.66	732.55±39.06
心臓重量/体重 (mg/g)	2.70±0.04	3.71±0.15**	3.24±0.08***
(左心室重量+中隔重量)/体重 (mg/g)	1.83±0.02	2.72±0.09**	2.37±0.07***

未負荷群に対して \*\*P < 0.01

普通食群に対して \*P < 0.05, \*\*P < 0.01

[0036] Furthermore, the heart was extracted from the rat after four-week breeding, and the operation over cardiac hypertrophy was investigated. A result is shown in Table 1. Formation of cardiac hypertrophy was intentionally controlled by sesamin administration by the rise list of blood pressure usually set to the diet group.

[0037] 21 example 2. SD system male rats (6 weeks old) were divided into three groups. Inner of three groups 2 groups extracted kidney of one of the two, from the one-week back, they administered DOCA (deoxycorticosterone acetate) hypodermically (15mg [kg] / and 2 times/(week)), made brine take in 1%, produced the DOCA salt hypertension model, and usually divided it into the diet group (seven animals) and the sesamin diet group (eight animals).

[0038] The feed of a diet group and a sesamin diet group usually used the same feed as an example 1. Remainder 1 group gave and bred general diet as a non-load group (six animals). It is tail cuff about the blood pressure of each group rat weekly. It measured using law. A result is shown in drawing 2. Furthermore, the heart was extracted from the rat after four-week breeding, and the operation over cardiac hypertrophy was investigated. A result is shown in Table 2.

[0039]

[Table 2]

表 2

	未負荷群	普通食群	セサミン食群
体重 (g)	421.83±8.42	331.43±12.23**	328.75±13.85**
心臓重量 (mg)	1101.67±31.14	1217.29±29.15	1056.62±60.49*
左心室重量+中隔重量 (mg)	739.67±20.90	932.00±22.07**	779.50±43.23**
心臓重量/体重 (mg/g)	2.61±0.05	3.71±0.18**	3.21±0.10***
(左心室重量+中隔重量)/体重 (mg/g)	1.75±0.03	2.84±0.14**	2.37±0.07***

未負荷群に対して \*\*P < 0.01

普通食群に対して \*P < 0.05, \*\*P < 0.01



[0040] From each group, from the rat of a suitable number, the thorax main artery and the intestinal tract film artery were extracted, and the operation over the vasoconstriction was investigated. The vasoconstriction carried out paraffin embedding of the thorax main artery and intestinal tract film artery which were extracted from each group after formalin fixation, and, in the thorax main artery, six places and an intestinal tract film artery produced three preparation (5 micrometers) from each blood vessel. It is each sample Elastica-Van-Gieson It dyed and the thickness of a blood vessel wall, blood vessel wall area and blood vessel wall area / inner-surface-of-cavity product ratio was investigated against the index using image-analysis equipment (IBASII, Carl Zeiss). A result is shown in Table 3.

[0041]

[Table 3]

表3 DOCA-Na高血圧モデルにおけるセサミンの血管狭窄に対する作用

	例数	血管壁の厚さ ( $\mu\text{m}$ )	血管壁面積 ( $\text{mm}^2$ )	血管壁面積/ 内腔面積比
胸部大動脈				
未負荷群	4	95 $\pm$ 1	0.41 $\pm$ 0.01	0.27 $\pm$ 0.01
普通食群	3	136 $\pm$ 5 ***	0.63 $\pm$ 0.04 **	0.35 $\pm$ 0.02 **
セサミン食群	5	107 $\pm$ 4 **	0.48 $\pm$ 0.03 *	0.28 $\pm$ 0.01 *
腸管膜動脈				
未負荷群	4	56 $\pm$ 1	0.12 $\pm$ 0.003	0.33 $\pm$ 0.02
普通食群	3	89 $\pm$ 2 ***	0.24 $\pm$ 0.01 ***	0.49 $\pm$ 0.02 **
セサミン食群	5	73 $\pm$ 3 **:	0.16 $\pm$ 0.01 **:.	0.42 $\pm$ 0.02 *

未負荷群に対して \*P<0.05, \*\*P<0.01, \*\*\*P<0.001

普通食群に対して \*P<0.05, \*\*P<0.01, \*\*\*P<0.001

[0042] The vasoconstriction was intentionally controlled by the rise of the blood pressure set to general diet, and the formation list of cardiac hypertrophy by sesamin administration.

[0043] The left renal artery was equipped with the silver clip (bore of 0.2mm) for the example 3.SD system male rat (weights 200-240g), 2K and 1C mold renal hypertension model were produced, and it considered as one groups [ seven ], and divided into six groups. One group gives general diet (the commercial type NMF, oriental yeast). The five remaining groups The patent (Japanese Patent Application No. 63-53642) for which it has already applied to general diet is followed. SESAMI Norian (compound A) prepared from purification sesame oil, the sesamol prepared from rough purification sesame oil (compound B), Moreover, 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, the 7-dioxabicyclo [3.3.0] octane (compound C), [0044] which were prepared from the acetone extract of a sesame seed 2, 6-screw - (3-methoxy-4-hydroxyphenyl) The -3, 7-dioxabicyclo [3.3.0] octane (compound D), 2-(3, 4-methylenedioxyphenyl)-6-(3-methoxy-4-hydroxy phenoxy)-3, and 7-dioxabicyclo [3.3.0] octane (compound E) was bred with each feed blended 1%. It is tail cuff about the blood pressure of after four weeks and a rat. It measured using law. A diet group's blood pressure rose to 185.4\*\*7.3 (mmHg), and has usually improved [ by giving compound A and the feed which blended B, C, D, and E ] to 151.3\*\*6.6, 159.7\*\*7.1, 163.2\*\*8.3, 156.4\*\*5.4 and 162.0\*\*5.9 (mmHg), respectively.

[0045] 2.4g of mixture of the derivative of this invention used for 100g of butterfats from which buttermilk was removed by churning actuation (churning) of an example 4. butter making process in the example 1 was added, \*\*\*\* actuation (working) was performed, and the butter which has the prevention or the improvement operation of hypertension which comes to add the active principle of this invention as an equal presentation was obtained.

[0046] 0.5g of derivatives of example 5. this invention was mixed with 20.5g of silicic acid anhydrides, and corn starch 79g was added to this, and it mixed further. 100ml of hide ROKISHI propyl cellulose ethanol solutions was added to this mixture 10%, and it \*\*\*\*(ed) as the conventional method, and extruded, and it dried and the granule was obtained.

7g of derivatives of example 6. this invention was mixed with 20g of silicic acid anhydrides, and microcrystal cellulose 10g, 3.0g of magnesium stearates, and 60g of lactoses were added to this, it mixed, this mixture was tableted with the single-engined type tableting machine, and 7mm of diameters and a tablet with a weight of 100mg were manufactured. [0047] The heating dissolution of the 2.5g of the derivatives of example 7. this invention was carried out at 122 degrees C at TO-10M (Nikko Chemicals)200g which is a nonionic surface active agent, 4.7975l. of sterilization physiological salines warmed at 60 degrees C at this could be added, and it agitated, and this was distributed to the vial in sterile, was sealed, and injections were manufactured.

Water is added to the example 8. gelatin 100 weight section and the food additive glycerol 35 weight section, and it dissolves at 50-60 degrees C, and is the viscosity of 20000cps. The gelatin coat was prepared. Next, 2% of mixture of the derivative of this invention used in 95.1% of wheat germ oils, 2.9% of vitamin-E oils, and the example 1 was mixed, and contents were prepared. Using these, capsule molding and desiccation were performed with the conventional method, and the software capsule containing 180mg [ per grain ] contents was manufactured. In this one grain of capsule, 3.6mg and 2.34mg of alpha-tocopherol were contained for the mixture of the derivative of this invention.

Example 9. cerebral apoplexy \*\*\*\*\* SHR (SHRSP) (a male, 8 weeks old) was made into one groups [ eight ], and it usually divided into two groups of a diet group and a sesamin diet group. A diet group usually gives commercial powder feed (Funabashi SP, Funabashi Farm), and a sesamin diet group is dioxabicyclo [3.3.0] of 0.5% this invention. The sesamin foods which blended the mixture (sesamin: 51.1%, episesamin:47.8%, and dioxabicyclo [3.3.0] octane derivative:1.1% of others) of an octane derivative were given. It bred for eight weeks and generating of an encephalomalacia blow hole was investigated in the effect and the list which are exerted on blood pressure, weight, and brain weight. A result is shown in Table 4. Although the encephalomalacia blow hole of SHRSP which the increment in brain weight is accepted in a diet group, and is usually a cerebral apoplexy lesion at a moiety was accepted, in a sesamin diet group, there is no increment in brain weight and generating of a cerebral apoplexy lesion was not accepted, either.

[0048]

[Table 4]

表 4

	普通食群	セサミン食群
体 重 (g)	2 5 5 ± 1 3	2 5 2 ± 4
血 圧 (mmHg)	2 6 7 ± 7	2 6 0 ± 7
脳重量 (g)	2. 0 2 ± 0. 0 9	1. 8 0 ± 0. 0 8
脳卒中発生率 (%)	5 0 (4 / 8) <sup>1)</sup>	0 (0 / 8)

<sup>1)</sup> 脳卒中ラット数 / 全ラット数

[Translation done.]